REMARKS

I. Status of the Claims

Claims 1-15, 29-31, and 33 will be pending in this application after the instant amendments are entered. Claims 16-28 and 32 had been previously cancelled. Claim 1 has been amended to recite that the "the membrane allows the retention of a portion of albumin in the presence of whole blood." This limitation finds support, for example, in paragraphs [0020] and [0048] of the specification (US 2006/0144782) and refers to the fact that not all of the albumin is lost when employing the membrane in the medical setting where it is intended to be used (*i.e.*, removal of toxic mediators in the treatment of, for example, systemic inflammatory response syndrome ("SIRS"), multiorgan system dysfunction syndrome ("MODS"), and/or multiorgan system failure ("MOSF")). New claim 33 is directed to the subject matter that has been instantly-deleted from claim 15. Accordingly, no new matter is added with these claim amendments.

II. Statement Regarding Substance of the Interview under 37 C.F.R. § 1.133(b)

Applicants thank Examiner Bass and Supervisor Menon for granting the interview held on August 9, 2010. At the interview, Applicants' representatives addressed the rejections over the cited art in the Office Action of February 23, 2010, discussed some possible claim amendments to further define the invention, and presented experimental data showing that the membranes of U.S. Patent No. 4,935,141 to Buck et al. ("*Buck*") do not possess the inherent properties attributed to them by the Office. Applicants will discuss the comparative testing presented at the interview in further detail below.

III. Rejections under 35 U.S.C. § 103

A. *Buck, Lee* and *Gorsuch*

The Office rejects claims 1, 3-13, and 29 under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 4,935,141 to Buck et al. ("*Buck*") in view of U.S. Patent No. 5,571,418 to Lee et al. ("*Lee*") as evidenced by U.S. Patent No. 6,802,820 to Gorsuch et al. ("*Gorsuch*"). Office Action, pages 2-4. The Office contends that "Buck discloses an asymmetric hollow fiber membrane . . . comprising . . . [a]t least one hydrophobic polymer . . . [a]t least one hydrophilic polymer . . . wherein said hydrophilic polymer is polyvinylpyrrolidone . . . [and a] three layer asymmetric structure (Fig. 1A-B) . . . ." *Id.*, page 2.

The Office relies on *Gorsuch* as evidence "that size exclusion limits and sieving coefficients can be easily manipulated based on test methods used to determine the size exclusion limits and sieving coefficients," and relies on *Lee* for its teachings of "membranes having molecular weight exclusion limits of between 100kD and 150kD." *Id.*

Applicants respectfully traverse this rejection and will explain below why the rejected claims are not obvious over the combination of *Buck*, *Lee* and *Gorsuch* for the reasons outlined below.

1. *Buck* does not inherently describe a membrane having the properties recited in the instant claims

Allowing passage of molecules of up to 45 000 Daltons

The Office argues that "[*Buck*] discloses the membrane allowing passage of molecules having a molecular weight of up to 45kD with a sieving coefficient of 0.1 to 1.0 (implicitly disclosed in col. 3, l. 65 - col. 4, l. 7 and col. 5, l. 46-54)." Office Action at 2. However, the cited disclosure in *Buck* is *completely silent* regarding Buck's membranes allowing passage of molecules having a molecular weight of up to 45kD. This information is not "implicitly disclosed" either.

The cited passages indicate that *Buck's* membranes "provide a high sieving coefficient (S) of at least about 0.6, e.g., between 0.6 and 0.8, for β_2-microglobulin, but at the same time provide a low sieving coefficient of albumin, of about 0.001." The fact that *Buck's* membranes allow passage of molecules having a molecular weight of about 11,500 Daltons (β_2-microglobulin) but exclude molecules with a molecular weight of about 68,000 Daltons (albumin) is not a disclosure, neither implicit nor explicit, of a membrane that "allows passage of molecules having a molecular weight of up to 45 000 Daltons." as instantly recited.

The fact that *Buck's* membranes do not inherently possess the instantly recited properties is further evidenced by the experimental data presented in the Declaration under 37 C.F.R. §1.132 of co-inventor Hermann Goehl ("Declaration") attached to this Response. For example, the Declaration compares the sieving coefficients *in vivo* of a commercial membrane that represents an embodiment of a membrane prepared according to the teachings in *Buck* ("High Flux" membrane, 170H, "*Buck's* membrane")

with a membrane of the instant invention (HCO 1100). Declaration at ¶ 8. The results are presented in graphical form in Figure 1. Figure 1 shows that *Buck's* membrane does not "allow[] passage of molecules having a molecular weight of up to 45 000 Daltons, with a sieving coefficient of 0.1-1.0 in presence of whole blood" as instantly recited. Rather, *Buck's* membrane displays a sieving coefficient for molecules having a molecular weight of up to 45 000 Daltons that is essentially zero. For at least this reason, *Buck* does not meet this limitation inherently and fails to support the instant rejection.

Exclusion limit of about 200kD with a sieving coefficient of 0.1 in water

The Office acknowledges that *Buck* "fails to explicitly disclose a membrane that has a molecular weight exclusion limit of about 200kD with a sieving coefficient of 0.1 in water." The Office argues, however, that because "Buck discloses a membrane with the same preferred structure as contained in Applicant's claims/specification; therefore, it is inherent that the membrane has such a property, absent evidence to the contrary (MPEP 2112)." Office Action, page 3. Applicants respectfully disagree.

Buck expressly states that the membrane according to its invention has an exclusion limit of the size of albumin or smaller:

> [I]n accordance with the present invention, the applicants have provided a selectively permeable asymmetric membrane [...] **the substantially uniform pore openings in the first layer having a size whereby proteins which have a molecular weight of at least that of albumin are substantially completely rejected** from the membrane.

Buck at col. 1, line 67, to col. 2, line 16 (emphasis added). Since albumin has a molecular weight of 68 kDa (see *Buck* at col. 5, line 39), *Buck*'s membrane therefore

has an exclusion limit of less than 68 kDa. Although this particular passage is silent as to whether the exclusion limit of less than 68 KDa is measured in water or in whole blood, *Buck* explicitly indicates that in the membranes of its invention "the difference between the sieving coefficients, measured in water (in vitro) and in plasma or whole blood (in vivo), respectively, is small." *Buck* at col. 6, ll. 3-6. This clearly shows that *Buck's* membrane does not have "a molecular weight exclusion limit of about 200,000 Daltons, with a sieving coefficient of 0.1 in water," as instantly recited.

Withdraw reliance on past arguments

Applicants no longer rely on the arguments presented in the response filed on February 12, 2010, at pages 4-5 regarding the disclosure in Figures 3 and 4 from *Buck* and EP 0 305 787, the European member of *Buck's* patent family. Therefore, Applicants ask the Examiner to no longer rely on those arguments when considering patentability of the instant claims.

2. Experimental data further demonstrates that *Buck's* membranes do not inherently have the same properties as those instantly claimed

The Office takes the position that "[*Buck*] discloses a membrane with the same preferred structure as contained in Applicant's claims/specification; therefore, it is inherent that the membrane has such a property, absent evidence to the contrary (MPEP 2112)." Office Action, page 3. Applicants respectfully disagree.

As demonstrated above and in the Declaration, *Buck's* membranes are not inherently the same as those of the instant invention. For example, the Declaration compares sieving coefficients and pore sizes for a commercial embodiment of a

membrane prepared according to *Buck* (e.g., P170H, as indicated in Table 1) and membranes according to the instant invention (e.g., HCO 1100, as indicated in Table 1).

Table 1 at pages 3-4 of the Declaration summarizes some of the differences in sieving coefficients in both plasma and water between the claimed membrane and a commercial membrane prepared according to *Buck*. As can be seen, the differences in sieving coefficients for myoglobin and albumin in both plasma and water are significantly different for both membranes. The difference in sieving behavior between the two membranes can be easily seen graphically in Figure 1 at page 5 of the Declaration. As mentioned before, the "High Flux" membrane is a commercial membrane prepared according to *Buck*, whereas the "HCO" membrane is a membrane according to the instant invention.

Applicants also direct the Office to Figure 3 in the Declaration at page 6, which shows electron micrographs of the surface of a "high-flux" membrane (such as the one prepared according to *Buck*), a high cut-off membrane (HCO, such as those presently claimed) and a plasma separation membrane, ("plasmafilter," such as the one in Figure 7 of *Gorsuch* included for comparison purposes). The photographs emphasize the differences between the micro-structure of the three types of membranes.

This experimental data clearly demonstrates that, contrary to the Office's contention, ***Buck's* membranes are different from those instantly claimed.**

The differences in sieving performance between membranes prepared according to *Buck* and those of the instant invention are not surprising given that the membranes are designed for different purposes. Membranes according to *Buck* are high-flux membranes (such as the commercially-available Gambro P170H dialyzer), used in

standard hemodialysis and are designed to remove small molecules, such as urea and creatinine, when the kidneys are in renal failure and are unable to cleanse the blood in a natural manner. In situations where a high-flux membrane is utilized, albumin loss needs to be extremely low because patients undergoing hemodialysis are normally treated on a routine basis and should be spared from the continuous loss of valuable proteins such as albumin.

In contrast, the instantly-claimed membrane is labeled as a "high cut-off" membrane and is designed to remove relatively larger proteins as they accumulate under certain extraordinary circumstances such as sepsis, or multiple myeloma. In such cases, patients would not undergo continuous dialysis treatment and the limited loss of albumin would be acceptable.

Figure 1 on page 5 of the Declaration demonstrates this fundamental difference between standard high-flux membranes, such as those disclosed in *Buck*, and high cut-off membranes such as those presently claimed. While both membranes allow for the passage of lower molecular weight compounds, such as inulin and vitamin B12, high-flux membranes generally have a cut-off in the range of 20-30kD in whole blood. That is, molecules with a molecular weight of about 25-30 kD can no longer pass through the membrane. Therefore, these membranes <u>will NOT allow for the passage of molecules in the range of 45 kD</u>. In contrast, membranes according to the present invention <u>WILL allow the passage of molecules in the range of 45 kD to the extent instantly claimed.</u> This behavior can be seen in the figure on page 2 of the Declaration.

This experimental data clearly demonstrates that the instantly-claimed membranes and those of *Buck* are different from each other in terms of structure and

sieving performance. The nature of these differences highlight the fact that knowledge of *Buck's* membranes would not have led one of ordinary skill in the art to modify them in order to arrive at the claimed invention.

3. *Gorsuch* and *Lee* do not demonstrate that sieving coefficients claimed are result effective variables

Relying on Figure 7 in *Gorsuch* to demonstrate that "molecular weight exclusion limits in water are deemed to be result effective variables," the Office states that the "size exclusion limits and sieving coefficients can be easily manipulated based on test methods used to determine size exclusion limits and sieving coefficients." Office Action, page 3. Applicants respectfully disagree.

Figure 7 of *Gorsuch* shows exemplary curves for sieving coefficients of different types of membranes. Applicants note that the curves do not seem to be based on actual data, but have been drawn to demonstrate the difference between high-flux membranes (shown in the left curve) and plasma separation membranes (shown in the right curve). Both of these membranes are different from those of the instant invention, as shown by the pore-size data in Figure 2 of the Declaration and the structure depicted in the accompanying micrographs. In any event, such membranes, as typically depicted in the figure, are different with regard to their composition, process for preparing them, structure, and use. *See*, *e.g.*, the Examples in *Gorsuch*. Accordingly, the different curves do not prove how sieving coefficients can be manipulated, but rather how very different sieving coefficients are associated with various types of membranes having different compositions, methods of preparation, etc.

Therefore, Figure 7 of *Gorsuch* does not show that "molecular weight exclusion limits in water are deemed to be result effective variables," as contended by the Office. Rather, as discussed above, Figure 7 merely demonstrates the differences between high-flux membranes and plasma separation membranes. *Gorsuch* actually confirms *Buck's* teaching that a membrane intended for hemodialysis has a sieving coefficient below 0.1 for proteins of 68 kD, and thus an exclusion limit of less than 68 kD. At best, *Gorsuch* shows that different membranes with different compositions and sieving characteristics are know in the art. *Gorsuch*, however, does not teach the skilled artisan how to manipulate the polymers of *Buck's* membranes so that the resulting membranes have the characteristics of the instantly-claimed invention.

Lee, in turn, discloses a membrane that is "capable of allowing passage of molecules up to 100,000 to 150,000 Daltons," and having a "sieving coefficient of about 1.0 for said toxic mediators," wherein the toxic mediators are defined as having a molecular weight "up to 60,000 to 70,000 Daltons." *Lee* at col. 3, ll. 41-45; col. 4, ll. 29-31, and ll. 49-52. Accordingly, *Lee's* membrane is significantly different from the currently claimed membrane. The claimed membrane does not have a sieving coefficient of 1.0 for molecules "up to 60,000 to 70,000 Daltons." The membrane disclosed by *Lee* is significantly more open than the presently claimed membrane, which has a sieving coefficient for molecules of 60,000 to 70,000 Daltons significantly lower than 1. *See, e.g.*, figure on page 2 of the Declaration.

If anything, *Lee* teaches that very open membranes are used to remove higher molecular weight compounds, including proteins such as albumin or interferons. This teaching leads one of ordinary skill in the art away from the instantly-claimed

membrane, which is a membrane designed to effectively allow the passage of middle molecules in the range of approximately 45 kD, but reduce to some degree the loss of proteins like albumin (68 kD) for already compromised patients.

Moreover, *Lee* is silent on the preparation of its membrane, and, therefore, along with *Buck* and *Gorsuch* does not give any guidance as to how to arrive at a membrane that "allows passage of molecules having a molecular weight of up to 45 000 Daltons with a sieving coefficient of 0.1 to 1.0" as instantly claimed. Accordingly, the combination of *Buck, Lee*, and *Gorsuch* fails to render the instant claims obvious. Therefore, Applicants respectfully request withdrawal of the rejection.

B. *Buck, Lee* and *Deppisch*

The Office rejects claim 2 under 35 U.S.C. § 103(a) as obvious over *Buck* in view of *Lee* and further in view of "Blood Material Interactions at the Surfaces of Membranes in Medical Applications," to Deppisch et al. ("*Deppisch*"). Office Action at 4. According to the Office, "Buck fails to explicitly disclose the size of hydrophilic domains on the membrane surface are in the range of 20-50nm," and relies on *Deppisch* for the teaching "that polyvinylpyrrolidone hemodialysis membranes such as those disclosed by Buck have hydrophilic domains in the range of 20-200 nm . . . ." *Id.* Applicants respectfully disagree and traverse the rejection.

Claim 2 is dependent from claim 1 and therefore encompass all the elements recited in claim 1. The shortcomings of *Buck* and *Lee* in making obvious the instant invention have already been discussed in previous sections. *Deppisch* does not overcome these shortcomings. Rather, as discussed in the previous Response, *Deppisch* confirms that the best membranes in the art at the time of the instant invention

were recognized to require a sieving coefficient for albumin of below 0.1, thus having a molecular exclusion limit of less than 68 kDa.

Accordingly, because *Deppisch* does not remedy the shortcomings of *Buck* or *Lee*, the proposed combination fails to meet the limitations of the instant claims. Accordingly, Applicants respectfully request that this rejection be withdrawn.

C. *Buck, Lee* and *Kawata*

The Office rejects claims 14, 15, 30, and 31 under 35 U.S.C. § 103(a) as obvious over *Buck* in view of *Lee* as further evidenced by European Patent No. 0 568 045 to Kawata et al. ("*Kawata*")[1]. Office Action, pages 4-5. Applicants respectfully disagree and traverse the rejection.

Kawata does not remedy the deficiencies of *Buck* and *Lee*. *Kawata* describes the preparation of another high-flux membrane such as the membrane described in *Buck*. *Kawata* is not concerned with the preparation of membranes for removal of high molecular weight molecules, but is focused on an improved membrane with regards to biocompatibility. *See* Abstract; *see also* page 2, ll. 30-33.

Accordingly, because *Kawata* does not remedy the shortcomings of *Buck* or *Lee*, the proposed combination fails to meet the limitations of the instant claims. Accordingly, Applicants respectfully request that this rejection be withdrawn.

[1] Applicants note that the first named inventor for European Patent No. 0 568 045 is Kawata, and not Kagawa.

IV. Conclusions

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: August 20, 2010

By: Kimberly D. Smith
Kimberly D. Smith
Reg. No. 63,219

Attachment: Declaration under 37 C.F.R. §1.132 of co-inventor Hermann Goehl, with Exhibits.